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# **Diabetes from humans to cats**

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43

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## **Abstract**

Diabetes mellitus is a common endocrinopathy in humans and in cats. The general prevalence of diabetes mellitus, and in particular of type 2 diabetes, has risen dramatically in recent years. This increase has often been linked to the rise in the obesity pandemic because obesity and the ensuing metabolic consequences constitute major risk factors for human type 2 and for feline diabetes. Feline diabetes shares many features of human type 2 diabetes in respect to its pathophysiology, underlying risk factors and treatment strategies. This review will briefly summarize major characteristics in the human and the feline disease and where available, point out the current knowledge on similarities and differences.

## **Human Type 2 Diabetes mellitus**

Human type 2 diabetes (T2DM) is a metabolic disorder which arises from the relative inability of the endocrine pancreas to meet increasing metabolic demands and to compensate for insulin resistance. Insulin resistance is a state of reduced responsiveness of insulin-target tissues to normal circulating levels of insulin. The degree to which glucose tolerance deteriorates in insulin-resistant individuals varies as a function of both the magnitude of insulin resistance and the capacity of the pancreas to adequately compensate for this defect. If insulin secretion fails to fully compensate, a condition of hyperglycemia despite hyperinsulinemia occurs. Hence, the worsening of insulin resistance together with abnormalities in compensatory insulin secretion and finally a failure of beta-cell function may eventually lead to the development of T2DM [58].

## **1 Epidemiology**

### **1.1 Genetics**

T2DM is a multifactorial disease influenced by heterogeneous factors including diet, physical activity, age and genes. Genetic predisposition is a key contributing factor in T2DM; the expression of a number of gene variants, including some genes encoding for transcription factors, enzymes involved in glucose metabolism proteins and molecules of the insulin signalling pathways, has been associated with islet cell dysfunction. However, none of the known genetic factors alone seems to be responsible for the vast majority of T2DM patients, despite the high overall heritability of T2DM [9].

### 1.2 Glucotoxicity and lipotoxicity

Among the several acquired factors that impair  $\beta$ -cell function, the role of glucose toxicity and lipotoxicity is of particular importance. The mechanism of  $\beta$ -cell loss is attributed to an increase in  $\beta$ -cell apoptosis that is not compensated by adequate regeneration. Chronic exposure to hyperglycemia has been shown to cause  $\beta$ -cell hypertrophy and eventually apoptosis; prolonged exposure of human and rodent  $\beta$ -cells to high glucose levels leads to increased production and release of interleukin-1 $\beta$  (IL-1 $\beta$ ) followed by  $\beta$ -cell specific up-regulation of the rate of apoptosis [36, 38].

Although fluctuations in free fatty acids (FFAs) levels are critical for normal insulin release, a prolonged increase in FFAs concentrations (lipotoxicity) is associated with impairments in insulin biosynthesis and glucose-stimulated insulin secretion. High levels of saturated FFAs, in particular palmitate, induce apoptosis independently from glucose in cultured human and rat islets [35, 37].

### 1.3. Amyloid deposition

Concurrent with the effects of hyperglycemia and hyperinsulinemia, abnormalities in amylin secretion, and in particular abnormalities in the processing of amylin and its local deposition as amyloid in the islets, may contribute to the progressive loss of  $\beta$ -cell

in T2DM. In humans, monkeys and cats, but not in mice or rats (which do not spontaneously develop a T2DM like syndrome), amylin has an amyloidogenic-promoting region, which resides within amino acids 20 to 29 of the 37 amino acid peptide hormone, and which predisposes amylin to aggregate and form pancreatic islet amyloid in the species named above. Islet amyloidogenesis involves the stepwise aggregation of monomers of amylin into oligomers, fibrils and, ultimately, mature amyloid deposits that can be observed under light microscopy. However, rather than these large amyloid deposits, the small amylin oligomers, which are formed in the early stages of fibril aggregation, might be the toxic principle responsible for amylin-mediated  $\beta$ -cell cytotoxicity and death. In fact, the toxicity of amylin oligomers seems to derive from the disruption and leakage of  $\beta$ -cell membranes due to the formation of ion channels/pore into the membrane [27, 44]. Further, the subsequent growth of amylin fibrils in the extracellular space impairs nutrients and oxygen uptake into the  $\beta$ -cell which in turn contributes to endoplasmic reticulum (ER) stress, and ultimately apoptosis [28].

## 2 Inflammation and diabetes

More recently, it has been proposed that inflammation might be the possible common mechanism embracing the effects of glucotoxicity, lipotoxicity and increased amyloid deposition on  $\beta$ -cell dysfunction in T2DM. This is suggested by the pathologically elevated levels of islet-derived cytokines, e.g. IL-1 $\beta$ , and the subsequent chemokines-mediated recruitment of macrophages observed in diabetic patients [11, 40].

The first evidence of a possible involvement of inflammation in diabetes can be traced back to more than a century ago [12] [62], however, it was only in 1993 that the

pioneering work by Hotamisligil and colleagues [23] causally linked inflammation to the pathogenesis of obesity, insulin resistance and T2DM. The revolutionary idea that adipose tissue-derived pro-inflammatory cytokines (e.g. tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ]) are overproduced by fat tissue of obese individuals and that these cytokines are able to induce insulin resistance in obese subjects, stimulated extensive research regarding the role of inflammation in the pathogenesis of insulin resistance, obesity and T2DM.

## 2.1 Inflammation and insulin resistance

Originally considered to be a passive lipid storage site, adipose tissue is now known to produce and secrete many signaling proteins that modulate many metabolic processes. These secretory products, known as “adipokines” or “adipocytokines, either directly or indirectly control triglyceride (TG) accumulation and differentiation of pre-adipocytes and initiate inflammatory responses in adipose tissue.

### 2.1.1 Adipokines

Primary adipokines (such as leptin and adiponectin) are produced primarily or exclusively by adipocytes.

The plasma leptin concentration correlates with body fat mass and increases and decreases in response to weight gain or weight loss, respectively, but leptin increases also more acutely in response to food intake [16]. Leptin stimulates  $\beta$ -oxidation of FA and inhibits lipogenesis in peripheral tissues; hence leptin functions to decrease TG content in these tissues and to decrease FA levels in the circulation.

In obesity, the physiological responses to leptin are diminished in the hypothalamus and possibly elsewhere, and leptin-target cells become resistant to its actions. The resistance to leptin’s effects in the hypothalamus and the concurrent lowering of the body's energy metabolism may lead to further weight gain in obese subjects. Resistance

to leptin action is often associated with severe insulin resistance as the result of increased ectopic fat accumulation and lipotoxic effects in insulin-sensitive tissues.

Adiponectin is produced exclusively by mature adipocytes and circulates in plasma in multimeric form, with the high molecular weight form being the most biologically active. Its secretion is stimulated by insulin and by dietary constituents such as amino acids. Adiponectin levels inversely correlate with fat mass, hepatic lipid content, dyslipidemia and insulin resistance. Adiponectin increases insulin sensitivity and influences glucose metabolism by increasing glycolysis and FA oxidation. Plasma levels of adiponectin are lower in subjects with obesity, T2DM, cardiovascular disease, hypertension, and metabolic syndrome compared to healthy patients.

#### 2.1.2 Adipocytokines

Among the numerous chemoattractant cytokines secreted by hypertrophied adipocytes in obesity, monocyte chemoattractant protein-1 (MCP-1) has the role to attract circulating monocytes to migrate into adipose tissue. These recruited monocytes mature into classically activated macrophages; by secreting TNF $\alpha$  and other cytokines such as IL-1 $\beta$ , they continue to attract more macrophages.

TNF- $\alpha$  and IL-6 plasma levels are elevated in obese humans and animals, and their production in visceral fat seems to be higher than in subcutaneous adipose tissue; this in principle is consistent with the more deleterious effect of visceral compared to subcutaneous fat accumulation. Both cytokines inhibit insulin action in adipocytes in part through serine phosphorylation of insulin receptor substrate (IRS) proteins which lowers their activity with the subsequent inhibition of insulin-stimulated glucose transport via GLUT4. In addition, the activation of inflammatory pathways contributes to induce and



propagate ER stress with detrimental consequences on insulin sensitivity and systemic metabolism [8].

### 2.1.3 Inflammatory lipid mediators

During prolonged caloric overload, the inappropriate accumulation of lipids in tissues other than fat, such as liver, skeletal muscle, heart and pancreatic  $\beta$ -cells, which rarely occurs under physiological conditions, overwhelms the capacity of the cells to oxidize fat and negatively affects the normal metabolic response and the functional integrity of the ER. By binding to Toll-like receptor-4 (TLR4) on adipose cells and macrophages, FFAs can directly drive the activation of the inflammatory signaling cascade via c-jun-NH2-terminal kinase (JNK) and NF- $\kappa$ B-I $\kappa$ B kinase (IKK $\beta$ ), which is directly linked to serine phosphorylation of IRS-1 and IRS-2 and to the impairment of insulin sensitivity and glucose transport [56]. Therefore, the “sensing” of saturated FFAs by TLR4 causes a classical activation of inflammatory pathways and contributes to the development of insulin resistance, suggesting a coupling between inflammation and insulin resistance, in the setting of obesity.

### 2.2 Inflammation and pancreatic $\beta$ -cell function

During infections and immunologic responses as well as during the metabolic syndrome, chronic metabolic stress may be responsible for the induction of a deleterious autoinflammatory process in pancreatic islets that eventually leads to a failure of insulin secretion and to T2DM. Recent findings suggest that the autoinflammation driven by increasing levels of glucose, FFA and IL-1 $\beta$  plays a causal role in the pathogenesis of T2DM [11]. In inflammatory states and in obesity, IL1 $\beta$  synthesis by resident macrophages in adipose tissue is increased. IL1 $\beta$ , leptin and FFA act directly on the  $\beta$ -

cells in pancreatic islets, inducing further transcription, translation and local release of IL1 $\beta$ . One of the master effects of IL1 $\beta$  is to induce the production of cytokines and chemokines from epithelial, endothelial and immunocompetent cells and therefore helps to increase the recruitment of macrophages into the islets. As a result, infiltrating macrophages enhance local IL1 $\beta$  production which, in a paracrine fashion, contributes to the induction of an autoinflammatory circuit in the  $\beta$ -cell inflammation. Increased local inflammatory responses cause  $\beta$ -cell failure and morphological destruction of the endocrine pancreas [10].

### **Feline diabetes mellitus**

Feline diabetes mellitus (FDM) closely resembles human T2DM in many features. The prevalence of diabetes in cats has increased enormously in the past years. In the United Kingdom, it has been suggested that nearly 1 in 200 cats is diabetic, and it has been estimated there are approximately 1 million diabetic cats in the United States. The development of complications in several organ systems including peripheral polyneuropathy and retinopathy, and the (relative) age of disease onset are also comparable to T2DM [30].

The typical diabetic cat is middle aged, usually older than 6 years of age, neutered, male and very often obese. Similar to human T2DM, environmental risk factors, such as physical inactivity and obesity, play the central role in the development and the increasing incidence of FDM. Polyuria, polydipsia, polyphagia, muscle wasting and weight loss are the most common clinical findings of FDM.

In diabetic cats the first phase of postprandial insulin release has been demonstrated to be delayed or absent; the second phase secretion usually is also delayed and sometimes exaggerated.

Despite the similar pathophysiology to human T2DM, insulin therapy is currently the most effective treatment to achieve glycemic control and to avoid life-threatening complications in diabetic cats. The reason why other treatment strategies such as oral antidiabetic drugs seem to be relatively less successful compared to humans may perhaps relate to the fact that FDM is often diagnosed at a later disease state than human T2DM.

### 3 Epidemiology

#### 3.1 Genetics

A breed predisposition seems to support the idea of a genetic component in the pathogenesis of FDM. In Burmese cats, one in 50 develops the disease whereas in domestic cats the frequency of FDM is only one in 200. The predisposition in Burmese cats is not sex linked or dominant [17].

#### 3.2 Obesity

Obesity in cats is generally defined as a 30% excess of body weight above normal; overweight animals are 10% to 15% above normal. In practice and in a clinical setting, it is often preferable to use a body condition score (BCS) system to classify body condition, overweight and obesity in cats. The prevalence of overweight cats, evaluated with BCS systems, is estimated to vary between 6% and 52% [7, 54, 55].

Like in humans, obesity in cats has been linked to detrimental effects on the health and longevity. It predisposes cats to the development of a multitude of diseases including

insulin resistance and feline diabetes, but also hepatic lipidosis, cardiorespiratory disease and others [68].

### 3.3 Neutering

Neutering has been shown to induce changes in basal metabolism and to be one of the major risk factors for feline obesity. Both male and female cats increase their food intake and body fat mass following neutering. Alterations in sex hormones seem to influence brain centers important for the control of food intake and metabolic rate and may result in increased energy intake and an overall positive energy balance [25, 39]. It has been demonstrated that gonadectomy removes the estrogenic inhibition of eating in female rodents and that these changes are reversed by estradiol treatment [14]. In principle, consistent with these reports, daily administration of estradiol prevents the increase in food intake following gonadectomy in both male and female overweight cats [6].

## 4 Pathogenesis of FDM

### 4.1 Insulin resistance

Inflammatory conditions may be an independent risk factor for insulin resistance and diabetes in cats but the causal implications have not yet been studied in detail. It has been reported that Burmese cats with chronic or recurring periodontal disease have impaired glycemic control and are more prone to develop diabetes [53].

In obese cats, insulin sensitivity is typically decreased by more than 50% compared to healthy lean animals [1] [19]; on average, diabetic cats have been found to be about six times less sensitive to insulin than healthy cats. In fact, each kilogram of weight gain reduces insulin sensitivity and glucose effectiveness in cats by 30% [20]. Insulin

resistance in diabetic cats can therefore be reversed by reducing body weight, similar to what has been observed in obese non-diabetic cats. [3]. Interestingly, obese male cats have lower innate insulin sensitivity and higher basal insulin concentrations; this may therefore be one factor explaining why obese male cats are more prone to diabetes than obese females [1].

#### 4.2 Glucotoxicity and lipotoxicity

By using long-term hyperglycemic and hyperlipidemic clamps in cats, it was possible to study the pathogenesis of  $\beta$ -cell dysfunction and loss induced by excess glucose or lipids *in vivo* under well controlled conditions [67]. We showed that severe  $\beta$ -cell dysfunction is rapidly induced by sustained hyperglycemia in cats. Sustained hyperglycemia strongly impaired  $\beta$ -cell function in cats, and this resulted in  $\beta$ -cell exhaustion and decreased insulin gene expression [67]. This study supported the hypothesis that hyperglycemia causes  $\beta$ -cell loss *in vivo*, as indicated by the 50% decrease in  $\beta$ -cell count per pancreatic area in glucose-infused cats. This was not compensated by increased  $\beta$ -cell proliferation. Based on histomorphological features, hyperglycemic cats had large parts of their islets devoid of nuclei. In most rodent studies, glucose infusion for 2–4 days either increased or had no effect on  $\beta$ -cell mass [50, 60], and none of these *in vivo* experiments demonstrated a demise of  $\beta$ -cells after infusion. We believe that these differing findings between cats and rodents may be due to the inherent species difference (e.g. different propensity for amylin to form islet amyloid which may interact with glucotoxic changes; see below) but other aspects such as the experimental design of the studies or their duration cannot be excluded at the time being.

As to the reason for the reduced number of  $\beta$ -cells in hyperglycemic cats, we found that apoptotic islet cells and  $\beta$ -cells positive for cleaved caspase-3 were only present in glucose-infused but not in control cats. Apoptosis may thus contribute to the reduced number of  $\beta$ -cells in hyperglycemic cats. In the islets isolated from hyperglycemic cats we found no increase in IL-8 or IL-1 $\beta$ , or the Fas receptor. Hence, in contrast to human islets exposed to high glucose [34, 38], apoptosis of  $\beta$ -cells in hyperglycemic cats may have occurred through mechanisms that do not involve local inflammatory reactions or Fas receptor upregulation.

In contrast to the detrimental effects of sustained hyperglycemia, hyperlipidemia leading to increased plasma levels of FFA did not affect basal insulin levels or glucose-stimulated insulin secretion in our experiment [67]. Conflicting results have been described with regard to the effects of excess free fatty acids on insulin secretion *in vivo*. Studies in rats and humans reported increased, decreased or unchanged  $\beta$ -cell function [15, 49, 59]. Hyperlipidemia and excess FFA levels in cats had no effect on  $\beta$ -cell number and  $\beta$ -cell apoptosis or proliferation. In cultured human and rat islets, exposure of  $\beta$ -cells to palmitate was toxic, whereas oleate protected from both palmitic- and glucose-induced  $\beta$ -cell apoptosis [35]. Some differences between our and other studies may partly be attributable to the different infusion protocols; in our case, we infused a lipid solution that was relatively low in saturated long chain fatty acids.

However, we found that both hyperglycemia and hyperlipidemia induced systemic inflammation in cats [67]. Hence, systemic inflammation may develop in diabetic cats similar to what has been described in human T2DM [61]. In contrast to T2DM in humans [13] and perhaps linked to the relative short duration of infusion, we did not observe an

inflammatory reaction in islets of hyperglycemic or hyperlipidemic cats, as assessed by islet transcripts of cytokines or chemokines and by the number of islet neutrophils.

#### 4.3 Amyloid deposition

More than 80% of diabetic cats seem to have pancreatic amyloid deposition. Depending on the extent of amyloidosis in diabetic cats, this seems to be associated with an approximately 50% loss of  $\beta$ -cells mass [33].  $\beta$ -cell vacuolar degeneration, chronic pancreatitis and a reduced number of islets or  $\beta$ - cells are other common histological findings in diabetic cat [47, 52]. However, not all cats with amyloid deposits develop diabetes [31] and amyloid deposits are also present in non-diabetic cats [32, 63]. In agreement with these findings, we recently observed that the mean amyloid-positive cross-sectional area in the pancreatic samples of 37 diabetic cats did in fact not differ from sex-, breed- and body weight- matched control cats (unpublished data) [64]; however, due to the retrospective nature of the study, the causal links could not be investigated.

#### 4.4 Inflammation and insulin resistance

As mentioned before, inflammation, particularly in adipose tissue, has been causally linked to diet- and obesity-related insulin resistance and to the development of T2DM in several human and rodent studies [21, 22, 57].

##### 4.4.1 Adipokines and adipocytokines

Similar to humans, secretion of adipokines like leptin and adiponectin from adipose tissue has been shown in cats [51]. Higher circulating levels of leptin positively correlate with insulin resistance; it was claimed that this may even occur independent of changes in body condition score and fat mass [2]. The association between increased

leptin levels and neutering is most probably related to the increase in fat mass gained post-neutering [39]. However, a causal inter-relationship between leptin, insulin resistance and diabetes has not been demonstrated in cats.

In cats, adiponectin is also produced and secreted exclusively by mature adipocytes; its gene expression is significantly higher in visceral than other adipose depots [24, 66]. Recent reports showed that the high molecular weight (HMW) multimers of adiponectin account for about 80% of total adiponectin in cats while HMW multimers only account for 30% of total adiponectin in humans [26, 29]. HMW multimers are more closely associated with insulin sensitivity and body fat mass than total adiponectin [29]. Plasma adiponectin concentrations negatively correlate with increases in fat mass, and circulating levels of adiponectin are significantly lower in obese than in normal-weight cats [20, 24, 46]. Further, it seems that total adiponectin levels are lower in obese neutered male than in female cats, although this gender difference may not be directly attributable to sex hormones levels. The role of adiponectin as anti-inflammatory adipokine has not been investigated in cats.

Several studies in cats have shown that TNF- $\alpha$  expression in adipose tissue and in skeletal muscle is increased in obese cats [18, 43]. However, there is a lack of published data regarding the circulation patterns of adipose-derived TNF- $\alpha$  and other cytokines in cats, probably due to the unavailability of reliable assays.

Gene expression of insulin signaling-related genes is decreased in insulin sensitive tissues of obese cats. To name a few examples, obese cats have decreased GLUT4 expression in muscle and fat [4], and IRS-2 mRNA levels are lower in skeletal muscle and liver [45].

#### 4.4.2 Inflammation and nutrient metabolism



In order to study some of the effects of inflammation on nutrient metabolism in cats, we recently performed an experiment where subacute inflammation was induced by 10 days of lipopolysaccharide (LPS) infusion, in the absence of obesity [48]. This manipulation was sufficient to cause a transient insulin resistance state at the whole-body level, and a long-lasting peripheral and tissue-specific insulin resistance in cats; both effects were observed in the absence of significant effects on pancreatic  $\beta$ -cell function. This is in principle agreement with findings in rats and humans, where the acute administration of LPS has been shown to impair insulin sensitivity but not pancreatic  $\beta$ -cell function [5].

LPS infusion also led to an increase of circulating and tissue markers of inflammation in cats [48]. Further, mRNA and protein analysis revealed that expression of key genes involved in glucose, lipid and insulin metabolism were altered in a manner consistent with a tissue-specific reduction in insulin sensitivity. Major changes were observed in adipose tissue and in particular in the subcutaneous fat depot. This included a reduced adipocyte size due to increased hormone sensitive lipase activity, decreased high density lipoprotein cholesterol levels and increased TGs levels in plasma and liver; all changes pointed to severe dyslipidemia. Among the many results, the observation that adipocyte size in both fat depots of LPS-infused cats was significantly decreased and that subcutaneous compared to visceral fat was found to exhibit a much higher expression of pro-inflammatory factors was particularly noteworthy. In fact, recent findings showed that in addition to adipose mass and distribution, mean fat cell size is associated with metabolic complications such as insulin resistance and adipose tissue inflammation in humans [42]. Further, it has been demonstrated that an increased proportion of small adipose cells in human subcutaneous adipose tissue is associated

with inflammation, independently of body mass index and insulin resistance [41]. Whether such factors play a role in cats is currently unknown.

#### 4.5 Inflammation and $\beta$ -cell function

Interestingly, both experimental hyperglycemia and hyperlipidemia induced a systemic inflammation in cats which resembled that observed in human T2DM [67]. However, in contrast to the findings in humans, local inflammatory reactions in the islets were not observed after the hyperglycemic or hyperlipidemic clamps in cats. Hence, although hyperglycemia (but not hypertriglyceridemia) had detrimental effects on the endocrine pancreas which resemble those observed in diabetes, these effects did not seem to depend on the activation of local inflammatory responses, at least during 10-day infusions of glucose or lipids, respectively. We also demonstrated that  $\beta$ -cell function was impaired during the initial days of endotoxin infusion but that this effect was no longer detectable by day 10 of the infusion [48].

Recently, we assessed whether diabetic cats have pathological evidence of islet inflammation or pancreatitis and found that the average counts of neutrophils, T- and B-lymphocytes in the islets did not differ between diabetic and healthy cats although the presence of lymphocytes in general tended to be more frequent in diabetic than control cats [64]. In addition, a subset of diabetic cats showed lymphocytic infiltration of the islets that might have contributed to  $\beta$ -cell loss. The results confirmed previous observations that loss of  $\beta$ -cells occurs in diabetic cats [33] and suggested that increased necrosis and fibrosis of the exocrine tissue may be associated with pancreatitis in at least some diabetic cats.

## Conclusions

396 In contrast to current rodent models, cats develop all aspects of the human  
397 disease including obesity-induced insulin resistance, impaired beta cell function,  
398 decreased number of  $\beta$ -cells and pancreatic amyloid deposition [1]. Therefore, cats are  
399 considered an interesting and perhaps the best non-primate available model to study the  
400 pathogenesis of human T2DM. Studies using cats may contribute to help developing  
401 preventive strategies and more targeted therapeutic approaches to investigate the  
402 pathogenesis of feline diabetes and, possibly, some of the mechanisms underlying  $\beta$ -  
403 cells dysfunction and decreased  $\beta$ -cells mass in T2DM in humans.

404 In clinical cases, an adequate control of glycemia in diabetic cats may result in  
405 clinical remission in about 40-80% of cases [65]. Remission likely depends on the  
406 remaining functionality and viability of  $\beta$ -cells in the pancreatic islets and the successful  
407 restoration of normoglycemia by the initial treatment. Because we showed that feline  $\beta$ -  
408 cells are very susceptible to the detrimental effects of excess glucose [67], rapid  
409 restoration of normoglycemia and drugs that promote  $\beta$ -cell function or prevent  
410 apoptosis may be tested in cats; such strategies may perhaps prevent  $\beta$ -cell toxicity or  
411 facilitate recovery from the toxic effects of hyperglycemia. In other words, an adequate  
412 control of glycemia may reverse glucose toxicity in the endocrine pancreas and restore  
413  $\beta$ -cells function and possibly  $\beta$ -cells mass.

414 Further, the tissue-specific insulin resistance and severe alterations in lipid  
415 metabolism induced by prolonged LPS infusion suggest that future efforts should  
416 concentrate on the study of the biological processes and the molecular mechanisms that  
417 underlie the tissue-specific development of inflammation and the related metabolic  
418 alterations in cats.

Based on the data available to date, it appears that inflammation may not be the primary mechanism involved in the development of  $\beta$ -cell dysfunction in cats. However, future studies are needed to clarify whether chronic concurrent infusion of lower doses of glucose and endotoxin might have a combined effect on  $\beta$ -cells that leads to the activation of the same inflammatory factors and ultimately mechanisms as in human T2DM.

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